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Airway obstruction, serum vitamin D and mortality in a 33-year follow-up study

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Abstract

Background and objective: Chronic obstructive pulmonary disease and low vitamin D status predict mortality, but their combined effect on mortality remains inconclusive. We aimed to investigate a joint effect of airway obstruction and vitamin D status on mortality in a nationally representative cohort.

Methods: We analysed data of 6676 Finnish adults participating between 1978 and 1980 in a national health examination survey, undergoing spirometry and having all necessary data collected. We followed them up in national registers through record linkage until 31 December 2011. We categorised the subjects with obstruction using the lower limit of normal (LLN) and the measured serum 25-hydroxyvitamin-D (s-25(OH)D) into tertiles.

Results: Both obstruction and low s-25(OH)D independently predicted mortality in a multivariate model adjusted also for age, sex, smoking, education, leisure physical activity, body mass index, asthma and serum C-reactive protein. However, a statistically significant ($p = 0.007$) interaction emerged: the adjusted mortality HRs (95% CI's) for s-25(OH)D in tertiles among the subjects without and with obstruction were 1.00 (lowest), 0.96 (0.87–1.05) and 0.89 (0.81–0.98); and 1.00, 0.96 (0.71–1.31) and 0.57 (0.40–0.80), respectively.

Conclusions: In conclusion, obstruction and low s-25(OH)D predict mortality independently of each other. Our findings suggest that low vitamin D status might be particularly detrimental among subjects with obstruction.

Introduction

Low vitamin D status and chronic obstructive pulmonary disease (COPD) are common underdiagnosed conditions worldwide. Inadequate exposure to sunlight and an insufficient intake from dietary sources induces a low vitamin D status, generally measured as serum 25-hydroxyvitamin-D (s-25(OH)D) concentrations (<30 nmol/L determined as deficiency). The prevalence of s-25(OH)D deficiency is currently up to 30% in Europe and 0.6% in Finland, yet over 30 years ago >20% of our study population suffered from a low s-25(OH)D (1-5). In COPD, a progressing airway obstruction primarily caused by smoking leads to early death. Globally, COPD prevalence is 10.1%, falling to 4.3% and 3.1%, respectively, among Finnish men and women (6-8).

Previous studies have shown both associations between COPD and low s-25(OH)D and between decreasing lung function measures and 25(OH)D concentrations (1,9-11). However, the link between COPD and vitamin D metabolism remains unconfirmed. As such, a low s-25(OH)D evidently plays a role in regulating inflammatory reactions in COPD (1,3,12). Low s-25(OH)D and COPD are associated with similar factors, such as ageing, a low socioeconomic status, smoking, physical inactivity and chronic diseases (1,3,6,13,14). Yet, limited longitudinal data exist on the association between COPD and low s-25(OH)D (12).

Low s-25(OH)D and COPD predict premature death—COPD by decreasing lung function and the s-25(OH)D by decreasing concentration (6,13-18). Whether low s-25(OH)D has a similar or different association with mortality in subjects with COPD than in general population remains less studied and inconclusive (19-21).

Thus, we aimed to analyse whether a low s-25(OH)D confounds or modifies the association between airway obstruction and mortality during a long follow-up.

Material and methods

Study population

The Mini-Finland Health Survey, a population-based nationally representative health examination survey, consists of a two-stage cluster performed between 1978 and 1980 (22). In all 40 nationally representative areas with 40 000 to 60 000 subjects living on them were selected for inclusion in the first stage; and a representative sample of Finnish adults (3637 men and 4363 women) aged 30 to 91 from each area was selected from the population register in the second stage. Each subject in the population of each area had an equal probability for selection (probability proportional to size sampling). From this sample, 7217 (90%) subjects participated in the survey. Our study included 6676 subjects (3091 men and 3585 women) for whom was collected all relevant health information and who underwent a comprehensive health examination, including spirometry (22-25).

Measurements and definition of determinants

Laboratory technicians with special training performed spirometry using a Vitalograph spirometer (Vitalograph Ltd., Buckingham, England) following standard guidelines and instructions. Technicians presented the test procedure individually to each subject. Ideally, each participant produced minimum two spirometry curves, as consistent as possible, reaching an adequate and high-quality forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC). The FEV_1/FVC was determined using the highest readings for FEV_1 and FVC from

101 the technically acceptable measurements for the air temperature and pressure, saturated with
102 water vapour (BTPS) values (spirometry technique used in Mini-Finland Health Survey).
103 Spirometry was performed without bronchodilation (22,23,25).

104 Individual lung function results were calculated using the Global Lung Function Initiative
105 (GLI) reference values which were derived from the spirometry records of 97,759 multi-
106 ethnic, healthy non-smokers aged 3 to 95. The GLI reference values were determined for four
107 separate ethnic groups, and we only applied the reference values for Caucasians. Subjects
108 with FEV_1/FVC values below the lower limit of normal (LLN) using reference values were
109 classified as having airway obstruction while others did not have obstruction (26,27).

110 Height and weight were measured. Body mass index (BMI) (weight (kg)/height^2 (m^2)) was
111 used as a measure of relative weight. Age, sex, leisure physical activity and educational levels
112 were collected through a basic questionnaire. Leisure physical activity was determined
113 through questions on the frequency, intensity and duration of physical activity and further
114 categorized as inactive (little physical exercise), occasionally active (exercise alongside some
115 hobbies or irregular exercise) and regularly active (regular exercise). The completed number
116 of years of schooling classified educational levels in basic (<8 years), intermediate (8–12
117 years) and higher (>12 years) (22-25).

118 A standard interview inquired smoking habits, and these were categorized as never, former
119 and current smokers. Former smokers had quit smoking minimum one month before the
120 baseline survey. All subjects who had smoked at least one pipe, cigar or cigarette daily or
121 almost daily during the year before the survey were categorised as current smokers. Current
122 smokers were further categorized into two groups based on the number of daily smoked
123 cigarettes: 1 to 19 and ≥20 cigarettes (22-25).

Fasting blood samples were taken during the health examination and stored frozen at −20°C. s-25(OH)D concentration was determined in 2003 using radioimmunoassay (DiaSorin, Inc., Stillwater, Minnesota, USA). The inter-assay coefficient of variation for s-25(OH)D determination was 7.80% at a mean level of 47.3 nmol/L (n = 167) and 9.12% at 131.3 nmol/L (n = 135). The proportion of quality-control samples was 13.5% (5,28). In this study, no single cut-off limit was used to define low s-25(OH)D. We classified s-25(OH)D concentrations into tertiles: 5–32 nmol/L, 33–48 nmol/L and 49–180 nmol/L; the concentrations approximated international definitions for vitamin D deficiency (<30 nmol/L) and insufficiency (30–49.9 nmol/L) (4).

In Finland, situated geographically between the latitudes 60°N and 70°N, biologically effective ultraviolet B irradiation producing vitamin D through the skin by sunshine is only possible during the summer months. When our baseline study was performed, s-25(OH)D concentrations were higher between May and October (2,5). Yet, baseline examinations were conducted during different seasons. Therefore, we divided subjects into two seasonal groups: winter (November–April) and summer (May–October).

Serum C-reactive protein (CRP) concentration was determined between 2003 and 2005 using a latex turbido-metric immunoassay (Olympus AU 400 analyser system for clinical chemistry, Wako Chemicals, Neuss, Germany), at a detection limit of 0.06 mg/L. The measured CRP levels were categorised as 0.04–0.99 mg/L, 1.00–1.99 mg/L and ≥2.00 mg/L (22,24).

Subject´s chronic disease history and their overall health status was inquired in the basic questionnaire. For those subjects who had any abnormal findings from the examination or questionnaires, a specially trained physician performed a standardised physical examination (22-24). The physician diagnosed asthma on the basis of medical history, symptoms and physical status applying preset criteria (22-25).

Follow-up

We continuously followed mortality from Statistics Finland using the subjects´ individual identification numbers to track participants from baseline examination through 31 December 2011 (29).

Statistical analysis

We constructed our models to analyse associations between obstruction and low s-25(OH)D primarily based on previous Finnish publications. As such, we previously analysed factors which were associated with obstruction in the same population sample (25) and others with s-25(OH)D in another Finnish data set (30,31). Factors which were associated with obstruction and s-25(OH)D previously included age, education (in years), leisure physical activity, BMI and smoking history. In addition, CRP and sex were associated with obstruction and s-25(OH)D in this material, and a history of asthma represented a possible confounding factor for obstruction. All these variables appeared relevant to our study; thus, we included them all in our analysis here. Additionally, we analysed the modifying effect of season of s-25(OH)D blood sampling (5,30,31).

We analysed the cross-sectional associations between obstruction and baseline characteristics using logistic regression, expressing results as model-adjusted odds ratios (ORs) with 95% confidence intervals (CIs). We analysed the strength of the associations of obstruction and s-25(OH)D with mortality in the cohort study design using Cox's proportional hazards regression model. The results were expressed as model-adjusted hazard ratios (HRs) with 95% CIs. We constructed three main models: adjusting for age and sex (1); further for

smoking (2); and finally also for leisure physical activity, education, BMI, asthma and serum C-reactive protein (3, multivariate model), which were also considered potential confounding factors. Whether s-25(OH)D, season of blood sample collection and obstruction modified the effects of each other were examined by entering their first-degree interaction terms into the multivariate models. Statistical significance was tested using the likelihood ratio test. Finally, to explore the proportional hazards assumption of the Cox's model and to test the adequacy of the long follow-up, we compared the results from the full model between the follow-up times of 0–10 years, 11–20 years and >20 years from baseline. In addition, we also restricted the follow-up experience to the years 2005 to 2011 to explore influence of the fortification of food with vitamin D that was introduced in Finland in 2003. We analysed s-25(OH)D as both categorical (tertiles) and ordinary-scaled variables throughout the study. All analyses were performed using SAS System for Windows (version 9.3, SAS Institute, Inc., Cary, NC, USA) and IBM´s SPSS (version 24).

Ethical considerations

The Mini-Finland Health Survey predated current legislation on ethics in medical research. However, all participants were fully informed about the study, participated voluntarily and the use of their information for medical research was explained to them. Agreeing to participate in the baseline health examination was considered informed consent. Statistics Finland approved the linkage of national mortality data to the survey data used here (29).

This study does not fall under the purview of laws regarding medical research, thus, the study protocol does not violate any ethical considerations or standards, according to a statement

from the Medical Ethics Committee of the Hospital District of Helsinki and Uusimaa in Finland (June 2013).

Results

Table 1 presents the baseline characteristics and their prevalence. At baseline, the cohort included 311 (4.7%) subjects with obstruction. Mean FEV_1 was 2.1 l/s (standard deviation (SD) 1.0) in obstructive and 3.3 l/s (SD 1.0) in non-obstructive subjects, while mean concentrations of s-25(OH)D reached 39.1 nmol/L (SD 18.8) and 43.6 nmol/L (SD 19.5), respectively.

We found an inverse association between obstruction and s-25(OH)D (Table 1). The season of blood sample collection did not modify that association (p=0.68 for the interaction).

By the end of 2011, 3530 (52.9%) deaths in the study population occurred, while 247 (79.4%) of the subjects with obstruction died. Obstruction and low s-25(OH)D independent of one another predicted mortality (Table 2). HR (95% CI) for the subjects with obstruction was 1.46 (1.28–1.68) when those without obstruction were used as the reference, while for s-25(OH)D from the lowest to highest tertile, HRs were 1 (reference), 0.92 (0.85–1.00) and 0.84 (0.78–0.92), respectively. Low s-25(OH)D did not confound the association between obstruction and mortality (Table 3).

A statistically significant interaction (p=0.007) emerged between obstruction and s-25(OH)D tertiles when entered as a categorical variable: among subjects with obstruction HR (95% CI) was 0.57 (0.40–0.80) in the third tertile, whereas among those without obstruction the corresponding HR was 0.89 (0.81–0.98) (Table 4). The season of blood sample collection did

not further modify or confound the associations of obstruction and s-25(OH)D with mortality (data not shown).

Finally, we used multivariate models to analyse the follow-up time strata of 0–10 years, 11–20 years and >20 years from baseline. The primary findings remained largely unchanged (data not shown). However, when the follow-up experience was restricted to the years 2005 to 2011 (21 deaths in 85 subjects with airway obstruction), the baseline s-25(OH)D did not anymore predict mortality (p-value for trend 0.32); HRs from the lowest to highest tertile were 1 (reference), 0.90 (0.76–1.07) and 0.88 (0.74–1.05), respectively.

Discussion

In our study airway obstruction and low s-25(OH)D independent of each other predicted mortality during the follow-up of 33 years. However, the association between low s-25(OH)D and mortality was stronger in those with obstruction than others.

In accordance with previous studies, we observed an inverse cross-sectional association between obstruction and s-25(OH)D, which was partly explained by other factors. COPD is evidently associated with low s-25(OH)D (1,9-11,14). Previously, vitamin D supplementation improved lung functions among ever-smokers with vitamin D-deficiency or COPD and decreased COPD exacerbations (32,33). Yet, the association between COPD and low s-25(OH)D is complex, multiple factors tend to confound it and previous findings appear contradictory (1,12). COPD and low s-25(OH)D have both shown associations with both chronic diseases and many factors predicting morbidity, such as ageing, smoking and reduced physical activity (1,3,6,13,30,34,35). Furthermore, low s-25(OH)D and s-25(OH)D

metabolites might affect COPD pathophysiology and co-morbidities, such as osteoporosis, cardiovascular diseases and respiratory infections (1,3,12,20).

In our study obstruction and low s-25(OH)D predicted mortality independently of each other and independently of other confounding factors. Comparisons of the results between previous studies and the present one are difficult because of the wealth of factors discussed above (1,3,6,12,13,30,34,35). In two studies with follow-up times from 10 to 14 years, low s-25(OH)D did not predict mortality among subjects with obstruction (19,20). Another study adjusted for common cardiovascular risk factors revealed an association between low s-25(OH)D and mortality among those with normal lung function (19). In a third study with an 18-year follow-up, low s-25(OH)D predicted mortality among the subjects with obstruction; however, this resulted primarily from the higher age and more negative cardiovascular risk factor profile of those with a low s-25(OH)D (21). In that study, the cut-off limit for the lowest s-25(OH)D tertile was <50.9 nmol/L which was much higher than our cut-off limit of <33 nmol/L.

In our study the association between low s-25(OH)D and mortality appeared pronounced among the subjects with obstruction. Albeit statistically significant, this interaction may result from chance alone because of small numbers of subjects. Nevertheless, if replicated in future studies, intervention trials and therapeutic implications may prove justified.

Our study's strength lies in its continuous 33-year follow-up of a population sample representing adult Finns from a national health examination survey with a 90% participation rate (22,23). Specially trained expert professionals performed examinations using standardised methods (22-24). The causes and dates of death were obtained from death certificates signed by the physicians responsible for their care (22,29). An additional strength lies in the naturally low s-25(OH)D in our study population; when the baseline survey was

executed, no vitamin D fortification was used and working outside in summertime under the sun remained common (22,23). The use of vitamin D supplements complicates and confounds analyses in newer datasets (1,3,12,30) whereas it rarely appeared among Finnish adults at the time of our baseline survey. In addition, the concentration of s-25(OH)D remains stable in long-term stored blood samples (36), although the 20 years between blood sampling and analyses might affect the s-25(OH)D concentrations measured.

The small sample size is the primary limitation in our study—our material carried no statistical power for more specific analyses. Therefore, such topics as the specific causes of death and degree of obstruction remain unanalysed. This same material resulted in previous publications regarding the influence of obstruction and s-25(OH)D, respectively, on cardiovascular and coronary mortality and the severity of obstruction and all-cause mortality (5,25,37). In addition, no bronchodilation test was performed; thus, we maybe have, incorrectly, categorised some reversible obstructions as chronic. Unfortunately, we had no data about COPD´s exacerbations and could, therefore, not consider this possible confounder. Additionally, no absolute definitions for COPD, obstruction or low s-25(OH)D exist, although clinicians use definitions and cut-off limits for both (2,4,6,27). Therefore, the results from studies (this and others) may not be directly comparable, a problem previously observed (3,10,37). There is remarkable seasonal and other variation in s-25(OH)D levels (38) but, unfortunately, only one blood sample was taken in our study. An additional limitation appears in the markedly improved s-25(OH)D among Finns between 2000 and 2011 resulting from the vitamin D fortification policy initiated after 2003 (2) and changes in smoking habits. However, the prevalence of obstruction remained unchanged in Finland between the Mini-Finland (1978–1980) and Health 2000 Surveys (7,39). Furthermore, other baseline

characteristics may have changed during follow-up exerting some influence on our results. This limitation typically accompanies cohort studies.

Conclusions

In conclusion, airway obstruction and low s-25(OH)D independently predict mortality; an outcome which a physician should consider when treating high-risk groups. If not replicated in future, the interaction we found for obstruction and low s-25(OH)D upon mortality does not justify causal inference.

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The University of Helsinki / Hospital District of Helsinki and Uusimaa awarded to the first author a Doctoral Candidate Position (from June 2016 to December 2017) which allowed for the write-up of our analysis.

Conflict of Interest

MD Mattila completed this study through financial support from the Hospital District of Helsinki and Uusimaa (a Doctoral Candidate Position in the Doctoral Programme of Clinical Research at the University of Helsinki / Hospital District of Helsinki and Uusimaa from June 2016 to December 2017). MD Vasankari, MSc Rissanen, PhD Knekt, MSc Sares-Jäske, MSc Jääskeläinen and MD Heliövaara declare no potential conflict of interest.

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The University of Helsinki / Hospital District of Helsinki and Uusimaa awarded to the first author a doctoral candidate position from June 2016 to December 2017.

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Table 1

Baseline characteristics and their associations with airway obstruction (FEV_1/FVC below LLN) in the study population from the logistic regression analyses

Characteristics		Total (n)	Obstruction (n)[1]	OR[2]	95% CI	OR[3]	95% CI
Vitamin D status[4]	First tertile (5–32 nmol/L)	2177	131	1		1	
	Second tertile (33–48 nmol/L)	2284	101	0.79	0.59–1.08	0.93	0.70–1.23
	Third tertile (49–180 nmol/L)	2215	79	0.61	0.44–0.85	0.75	0.55–1.02
p (for trend)				0.001		0.07	
Age (in years)	Mean 50.5, SD ± 13.7[5]		311	1.67	1.50–1.88	1.66	1.45–1.89
p (for trend)				<0.001		<0.001	
Sex	Male	3091	207	1		1	
	Female	3585	104	0.38	0.30–0.48	0.58	0.43–0.79
p (for heterogeneity)				<0.001		<0.001	
Smoking	Never smoker	3690	92	1		1	
	Former smoker	1388	79	2.03	1.43–2.88	2.20	1.54–3.15
	Current smoker, 1–19 cigarettes/day	991	83	3.90	2.77–5.48	3.42	2.39–4.90
	Current smoker, ≥20 cigarettes/day	607	57	4.81	3.23–7.17	4.41	2.91–6.70
p (for heterogeneity)				<0.001		<0.001	
Asthma	No	6558	280	1		1	
	Yes	118	31	8.82	5.65–13.78	11.43	7.11–18.36
p (for heterogeneity)				<0.001		<0.001	
Leisure physical activity	Inactive	2349	155	1		1	
	Occasionally active	3279	133	0.65	0.51–0.82	0.78	0.61–1.01
	Regularly active	1048	23	0.36	0.23–0.57	0.51	0.32–0.82
p (for heterogeneity)				<0.001		0.009	
Educational level	Basic	4480	261	1		1	
	Intermediate	1431	33	0.48	0.33–0.70	0.51	0.35–0.75
	Higher	765	17	0.49	0.30–0.82	0.56	0.33–0.94
p (for heterogeneity)				<0.001		<0.001	
BMI	<20	310	32	1		1	
	20–24.99	2733	135	0.39	0.26–0.59	0.43	0.27–0.67
	25–29.99	2632	105	0.26	0.17–0.40	0.28	0.18–0.45
	30–34.99	826	32	0.26	0.15–0.44	0.26	0.15–0.45
	≥35	175	7	0.35	0.15–0.82	0.32	0.13–0.78
p (for trend)				<0.001		<0.001	
CRP[6]	0.04–0.99 mg/L	3180	107	1		1	
	1–1.99 mg/L	1528	77	1.26	0.93–1.71	1.22	0.89–1.68
	≥2.00 mg/L	1968	127	1.43	1.09–1.88	1.16	0.86–1.55
p (for trend)				0.01		0.35	

[1] FEV_1/FVC below LLN.

[2] Odds ratio (OR) with 95% confidence intervals (CIs), age adjusted for sex, sex adjusted for age and the other factors adjusted for age and sex.

[3] OR with 95% CIs in a multivariate model adjusted for all factors listed in this table.

[4] Concentration of 25-hydroxyvitamin D (25(OH)D) in tertiles

[5] SD, standard deviation; range 61, 30–91 years.

[6] Concentration of C-reactive protein.

Table 2

Associations between baseline characteristics and mortality from 1978–1980 through 31 December 2011

Characteristics		Deaths (n)	HR[1]	95% CI	HR[2]	95% CI
Obstruction[3]	No	3283	1		1	
	Yes	247	1.68	1.48–1.92	1.46	1.28–1.68
p (for heterogeneity)			<0.001		<0.001	
Vitamin D status[4]	First tertile (5–32 nmol/L)	1331	1		1	
	Second tertile (33–48 nmol/L)	1165	0.89	0.82–0.96	0.92	0.85–1.00
	Third tertile (49–180 nmol/L)	1034	0.77	0.71–0.84	0.84	0.78–0.92
p (for trend)			<0.001		<0.001	
Age	Years, ±1 SD	Mean 59.0, SD ± 12.2, Range 61[5]	4.42	4.23–4.63	4.49	4.28–4.71
p (for trend)			<0.001		<0.001	
Sex	Male	1759	1		1	
	Female	1771	0.54	0.51–0.58	0.63	0.58–0.68
p (for heterogeneity)			<0.001		<0.001	
Smoking	Never smoker	1845	1		1	
	Former smoker	748	1.12	1.02–1.23	1.12	1.01–1.23
	Current smoker, 1–19 cigarettes/day	563	1.86	1.68–2.06	1.72	1.55–1.91
	Current smoker, ≥20 cigarettes/day	374	2.73	2.41–3.09	2.35	2.06–2.67
p (for heterogeneity)			<0.001		<0.001	
Asthma	No	3456	1		1	
	Yes	74	1.05	0.83–1.32	0.95	0.75–1.20
p (for heterogeneity)			0.70		0.68	
Leisure physical activity	Inactive	1498	1		1	
	Occasionally active	1623	0.78	0.72–0.83	0.87	0.81–0.94
	Regularly active	409	0.69	0.62–0.77	0.87	0.78–0.98
p (for heterogeneity)			<0.001		<0.001	
Educational level	Basic	2750	1		1	
	Intermediate	559	0.87	0.79–0.95	0.92	0.84–1.01
	Higher	221	0.68	0.59–0.78	0.73	0.64–0.84
p (for heterogeneity)			<0.001		<0.001	
BMI	<20	138	1		1	
	20–24.9	1174	0.59	0.50–0.71	0.63	0.53–0.75
	25–29.9	1514	0.61	0.51–0.72	0.65	0.54–0.78
	30–34.9	576	0.74	0.62–0.90	0.74	0.61–0.89
	≥35	128	0.86	0.68–1.10	0.78	0.61–1.00
p (for trend)			0.005		0.196	
CRP[6]	0–0.99 mg/L	1234	1		1	
	1–1.99 mg/L	913	1.22	1.12–1.33	1.15	1.05–1.26
	≥2 mg/L	1383	1.67	1.54–1.80	1.46	1.35–1.59
p (for trend)			<0.001		<0.001	

[1] Hazard ratio (HR) with 95% confidence intervals (CIs), age adjusted for sex, sex adjusted for age and other factors adjusted for age and sex.

[2] HR with 95% CIs in a multivariate model adjusted for all factors listed in this table.

[3] FEV_1/FVC over or below LLN.

[4] Concentration of 25-hydroxyvitamin D (25(OH)D) in tertiles.

[5] SD, standard deviation; range 30–91 years.

[6] Concentration of C-reactive protein.

Table 3

Association between airway obstruction (FEV_1/FVC below LLN) and mortality[1] in variously adjusted models from 1978–1980 through 31 December 2011

Model adjusted for		**HR[2]**	**95% CI**
Age and sex	No obstruction[3]	1	
	Obstruction[3]	1.69	1.49–1.93
Age, sex, vitamin D status[4]	No obstruction[3]	1	
	Obstruction[3]	1.68	1.48–1.92
Age, sex, smoking history	No obstruction[3]	1	
	Obstruction[3]	1.53	1.34–1.74
Age, sex, smoking history, vitamin D status[4]	No obstruction[3]	1	
	Obstruction[3]	1.52	1.33–1.73
Full model[5], without vitamin D status[4]	No obstruction[3]	1	
	Obstruction[3]	1.46	1.27–1.67
Full model[5]with vitamin D status[4]	No obstruction[3]	1	
	Obstruction[3]	1.46	1.28–1.67

[1] There were 3283 deaths in subjects without obstruction and 247 in those with obstruction.

[2] Hazard ratio (HR) with 95% confidence intervals (CIs).

[3] FEV_1/FVC over or below LLN.

[4] Concentration of 25-hydroxyvitamin D (25(OH)D) in tertiles.

[5] Multivariate model adjusted for age, sex, smoking, obstruction, asthma, education (in years), leisure physical activity, BMI and CRP.

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Table 4

Association between airway obstruction (FEV_1/FVC below LLN), vitamin D status and mortality from 1978–1980 through 31 December 2011

Characteristics	**No obstruction**				**Obstruction**			
Vitamin D status[1]	Total (n)	Deaths (n)	HR[2]	95% CI	Total (n)	Deaths (n)	HR[2]	95% CI
First tertile (5–32 nmol/L)	2046	1220	1		131	111	1	
Second tertile (33–48 nmol/L)	2183	1083	0.96	0.87–1.05	101	82	0.96	0.71–1.31
Third tertile (49–180 nmol/L)	2136	980	0.89	0.81–0.98	79	54	0.57	0.40–0.80
p-value for trend				0.002				0.002
p-values for interactions 'obstruction*vitamin D status'								
Vitamin D status as an ordinary scaled variable:				0.02				
Vitamin D status as a categorical variable:				0.007				

[1] Concentration of 25-hydroxyvitamin D (25(OH)D).

[2] HR with 95% CIs in multivariate model adjusted for age, sex, smoking, obstruction, asthma, education (in years), leisure physical activity, BMI and CRP.